Amendments to the Specification:

Please replace the BRIEF DESCRIPTION OF DRAWINGS starting at page 5, line 10 to page 7, line 17, with the following amended BRIEF DESCRIPTION OF DRAWINGS:

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 A-B is a diagram showing the amino acid sequences of the H chain (SEQ ID NO: 7) and L chain (SEQ ID NO: 8) variable regions of anti-human TNFα mouse neutralizing antibody 3B10. Amino acids are indicated by the one-letter notation method and numbered in accordance with the method of Kabat et al. (US Dept. Health and Human Services, US Government Printing Offices, 1991). The underlined parts indicate the CDRs determined in accordance with the method of Kabat et al. (US Dept. Health and Human Services, US Government Printing Offices, 1991), while the bordered parts indicate the CDRs determined in accordance with the method of Chothia et al. (J. Mol. Biol. 196, 901, 1987). In the present invention, amino acids belonging to either of these CDRs are regarded as "CDR". For reference, the amino acid sequences of the H chain and L chain variable regions of HBS-1 antibody corresponding to the sequences of 3B10 are also provided.

Fig. 2 A-B provides model views of expression vectors for a human/mouse chimeric antibody against human TNFα. The vector A is an expression vector for the H chain of the human/mouse chimeric antibody against human TNFα, while the vector B is an expression vector for the L chain of the human/mouse chimeric antibody against human TNFα. In this figure, VH stands for the variable region of

the H chain; SH stands for the signal region of the H chain; CH1, CH2 and CH3 stand respectively for 3 constant regions of the H chain; VL stands for the variable region of the L chain; SL stands for the signal region of the L chain; and CL stands for the constant region of the L chain.

Fig. 3 A-B provides diagrams showing procedures for constructing humanized anti-human TNFα antibodies. In this figure, the positions marked with figures and asterisks represent the positions wherein amino acids in the h3B10-1 frameworks have been substituted by amino acid residues of mouse 3B10. L1 to L6 stand respectively for PCR primers employed in constructing the L chain of h3B10-1, while H1 to H6 stand respectively for PCR primers employed in constructing the H chain of h3B10-1. This method is performed in accordance with an already reported method (Cancer Res. 53, 851, 1993).

Fig. 4 A-B provides graphs showing the affinities of humanized anti-human TNFα antibodies for human TNFα. Specifically, these graphs show the affinities of the culture supernatants of COS-1 cells, into which genes encoding respective humanized anti-human TNFα antibodies have been transferred, 48 hours after the gene transfer. First, IgG having human IgG Fc is quantified by the FCA method. Then, the affinity of each humanized anti-human TNFα antibody for human TNFα is examined at various IgG concentrations by the ELISA method. The data are expressed in terms of absorbance at 450 nm.

Fig. 5 A-B provides graphs showing the affinities of humanized anti-human TNFα antibodies for human TNFα. Specifically, these graphs show the affinities of the culture supernatants of COS-1 cells, into which genes encoding respective humanized anti-human TNFα antibodies have been transferred, 48 hours after the

gene transfer. First, IgG having human IgG Fc is quantified by the FCA method. Then, the affinity of each humanized anti-human TNFα antibody for human TNFα is examined at various IgG concentrations (A) or at 1.0 ng/ml (B) by the ELISA method. The data are expressed in terms of absorbance at 450 nm. In (B), the data are expressed in terms of mean ± standard deviation.

Please replace the paragraph starting at page 16, line 17 and ending at page 17, line 20 with the following amended paragraph:

The total RNA of 3B10 cells (J. Immunol. Methods 96, 57, 1987) secreting a mouse monoclonal antibody against human TNFα was separated using an RNAzol B reagent (manufactured by BIOTEX Laboratories). Using this total RNA, cDNAs were synthesized with the use of a random hexamer and a reverse transcriptase (~~Super Script~~ SUPER SCRIPT ™ Preamplification System, manufactured by GIBCO BRL). From among the cDNAs thus obtained, cDNAs encoding the H chain and L chain variable regions were amplified by the polymerase chain reaction (PCR) method. The cDNA of the L chain variable region was amplified using amplification primers synthesized according to the sequences reported by Huse et al. (Science 246, 1275, 1989), while the cDNA of the H chain variable region was amplified with the combined use of a 5'-primer (5'-AGGTGAAGCTNGTGGAG/ATCTGG-3') designed based on the H chain amino acid sequence reported by Kabat et al. (US Dept. Health and Human Services, US Government Printing Offices, 1991) and a 3'-primer of Huse et al. A thermostable DNA polymerase (~~AmpliTaq~~ AMPLITAQ® DNA

polymerase, manufactured by Perkin-Elmer) and a thermal cycler (TRIO-Thermo-block, manufactured by ~~Biometra~~ BIOMETRA® were used for the PCR. The nucleotide sequences of the cDNAs thus obtained were analyzed in accordance with the method of Sanger et al. (Proc. Natl. Acad. Sci. USA 74, 5463, 1977). Fig. 1 shows the nucleotide sequences of the H chain and L chain variable regions of the 3B10 antibody thus obtained. The CDRs were then identified in accordance with the method of Kabat et al. (US Dept. Health and Human Services, US Government Printing Offices, 1991) or the method of Chothia et al. (J. Mol. Biol. 196, 901, 1987). In the present invention, an amino acid sequence contained in any of the CDRs is referred to as a "CDR".

Please replace the paragraph starting at page 20, line 27 and ending at page 21, line 12 with the following amended paragraph:

Eight humanized 3B10 antibody derivatives were produced by further mutating h3B10-1. Mutations were introduced into the H chain and L chain framework regions. Specifically, h3B10-1 was employed as a template and PCR was carried out using primers carrying introduced mutations. A thermostable DNA polymerase (~~AmpliTaq~~ AMPLITAQ® DNA polymerase, manufactured by Perkin-Elmer) and a thermal cycler (TRIO-Thermo-block, manufactured by ~~Biometra~~ BIOMETRA®) were used in the PCR. Table 2 summarizes the differing points of the amino acid sequences of the produced 8 humanized antibodies (named h3B10-2 to 9), h3B10-1H and h3B10-1L. The antibody having the same L chain as h3B10-1

and the actual H chain framework regions of HBS-1 was named h3B10-1H, while the antibody having the same H chain as h3B10-1 and the actual L chain framework regions of HBS-1 was named h3B10-1L.

Please replace the paragraph starting at page 22, line 20 and ending at page 24, line 2 with the following amended paragraph:

3.0×10^5 COS-1 cells (obtained from ATCC) were inoculated into a 35 mm Petri dish and precultured for 18 hours. Two μg portions of the pairs of respective H chain expression vectors and L chain expression vectors corresponding to the humanized anti-human TNFα antibody and the human/mouse chimeric antibodies constructed in Examples 2 to 4 (i.e., 9 types in total) were simultaneously transferred into the COS-1 cells using 10 μl of a ~~Lipofectamine~~ LIPOFECTAMINE™ Reagent (manufactured by GIBCO BRL). The affinities for human TNFα of the recombinant antibodies secreted from the gene-introduced cells were examined by the ELISA method. Also, the human IgG in the culture supernatant was quantified by the fluorescence concentration analyzer (FCA) method. The ELISA method was carried out in the following manner. First, 60 wells at the center of a 96-well plate were filled with 10 μg/ml human TNF-α which was then immobilized by incubating at room temperature for 18 hours. After washing with a washing buffer (phosphate buffered saline (PBS) containing 0.1% ~~Tween~~ TWEEN® 20) three times, the wells were blocked with PBS containing 1% of BSA for 2 hours. After washing with PBS-T three times, the human TNF-α was reacted with each of the COS-1 cell culture

supernatants for 2 hours. After washing in the same manner, the antibody binding with TNF-α was reacted with peroxidase-labeled goat anti-human IgG Fc antibody (manufactured by Jackson ImmunoResearch Laboratories) or peroxidase-labeled goat anti-mouse IgG Fc antibody (manufactured by Caltag Laboratories) and detected in accordance with the method proposed in the literature (J. Immunol. Methods 143, 89, 1991). Separately, the FCA method was carried out in accordance with an already reported method (Biochem. Biophys. Res. Commun. 193, 886, 1993) using FCA particles coated with goat anti-human IgG Fc antibody and FITC-labeled goat anti-human IgG Fc antibody. Quantification was performed by using human IgG of a known concentration as the standard. The affinity for human TNFα of each humanized antibody expressed in the COS-1 cells was represented as ELISA reaction doses at various IgG concentrations.